REMARKS

Claims 1 – 16, 21 and 22 are presently before the examiner.

35 USC § 112, first paragraph rejection of claims 1- 16, 21 and 22

(a) The examiner has rejected claims 1 – 16, 21, and 22 under §112, first paragraph, because NADP was inadvertently identified in claim 16 and on Page 7, line 26 as "nicotinamide diphosphate" instead of "nicotinamide adenine diphosphate."

(b) The examiner also rejected claims 1 – 16, 21 and 22 under § 112, first paragraph, in that the examiner is of the opinion that there is a contradiction in the specification, namely, on page 18 lines 5 – 6, it is stated that "using methotrexate (Amethopterin), which is not a dihydrofolate reductase inhibitor," on page 18, lines 12 – 14 it is stated that "were stained indicating that, as expected, methotrexate failed to inhibit dihydrofolate reductase, the biochemical pathway for which the histochemical reagent was designed was intact and TNBT was reduced to its colored form." Then the examiner states "Methotrexate is a known dihydrofolate, which contradicts the statement in the specification, see SIGMA Catalogue page 97."

Applicant's response

(a) The claim and the specification have been amended to correct the inadvertent omission of the word "adenine" when presenting the full name of NADP. Since NADP is a standard designation for a common biochemical compound and is well-known to all skilled in the art as such, the amendment does not add new matter. All skilled artisans would immediately recognize the error in context and substitute the correct name of the compound. The examiner is requested to withdraw the rejection.

(b) The methotrexate example, which is not necessary to support the claims in terms of description or enablement, has been removed from the specification rendering the matter moot. However, an explanation would appear to be in order:

Methotrexate is indeed indicated in the Sigma catalogue to be a dihydrofolate reductase inhibitor. Upon addressing this with the applicant, it became apparent that there had been a miscommunication between him and myself with regard to the methotrexate example. Applicant was fully aware of the fact that methotrexate was "known" to be a dehydrofolate reductase inhibitor, so he was somewhat nonplused with

the observed result, i.e., that the cells stained indicating the opposite: that methotrexate did not appear to inhibit the reductase in his test. In follow up experiments, applicant determined that methotrexate does not directly inhibit dehydrofolate reductase. Rather, what appears to be happening is that methotrexate is a competitive substrate for the reductase. Since it is not actually inhibited by methotrexate, the reductase performs "normally" using methotrexate as a substrate and producing the same cofactor that is produced if dihydrofolate were the substrate. The cofactor then reacts as expected with applicant's histochemical reagent, resulting in stained cells. Applicant further determined that methotrexate appears to have an affinity for the reductase that is upwards of three orders of magnitude greater that the affinity of the natural substrate, dihydrofolate. So, when both are present, methotrexate preferentially binds to and reacts with the reductase, resulting in gross inhibition of the biochemical pathway since the dihydrofolate/reductase product is not available for the next step of the biochemical pathway.

Again, the above explanation is provided merely to apprise the examiner of the miscommunication between myself and applicant. As stated previously, the methotrexate example has no §112 bearing whatsoever on the claims and its removal eliminates the confusion noted by the examiner. The examiner is requested to withdraw the rejection.

35 USC § 112, first paragraph rejection of claims 1 – 15, 21 and 22

The examiner has rejected claims 1- 15, 21 and 22 under § 112, first paragraph in that, in the examiner's opinion, the specification does not reasonably provide enablement for the broad claimed inventions in view of the fact that the test will not give suitable results based on the claimed language. The examiner states that "One of ordinary skill in the art would obtain erroneous results based on the fact that the test depends on the concentration of the reagents which may give a positive chromogenic test if the concentration of the antibiotic is not sufficient to interact with the enzyme but the enzyme is still susceptible to the antibiotic." Applicant traverses.

Applicant's response

As indicated in the specification, the test is intended for clinical use. The example, however, was a laboratory proof-of-principle and not intended to be a clinical

protocol. A clinician attempting to determine if a particular pathogen is or is not susceptible to a particular antibiotic would, without question, initially perform the test using one dose, the maximum labeled dose, of the antibiotic. If staining is observed, no further testing is required; the pathogen is not sufficiently susceptible to the antibiotic use it. If no staining is observed, then dilution tests could be performed to determine the minimum dosage that would be effective.

The examiner is requested to withdraw the rejection.

35 USC § 102(b) rejection of claims 1 – 5, 7,8, 21 and 22

The examiner has rejected claims 1 – 5 , 7, 8, 21, and 22 under § 102(b) as being anticipated by Watson, et al., U.S. Pat. No. 5,998,159. The examiner cites column 1, lines 10 – 11, "methods for high throughput screening for compounds with antibiotic activity," column 2, lines 33 – 34, "The compounds are then administered in conjunction with known antibacterial agents. This technique is currently being tested for treating organisms resistant to tetracycline compounds," column 2, lines 45 – 67 drawn to sulfonamide antibiotics, columns 13 – 14, 19 –22, column 24 lines 54 – column 26 and the examples in column 29 – 31, line 42 "anticipates the claimed inventions which employs a chromogenic compound to form a chromogenic color when the bacteria is not susceptible to antibiotics which disclosures are within the scope of the claimed invention." Applicant traverses.

Applicant's response

The quote from column 1, lines 10 – 11 is simply a statement of purpose by Watson, et al., that is, that the patent is directed to a method of screening compounds (whose activity is unknown) to see if they have antibiotic activity. This purpose is opposite to that of the present invention, which relates to testing <u>known clinical</u> antibiotics against a pathogenic organism (whose identity may be unknown) isolated from an infected patient to determine if the organism is susceptible to the antibiotic.

The quote from column 2, lines 33 – 34 is taken from a description of an approach to overcoming resistance to antibiotics, tetracycline in particular, that is, the use of compounds that attack the resistance mechanism to allow tetracycline to have its intended effect. Again, this has no bearing on the present invention.

The quote from column 2, lines 45 – 47 is simply a description of the mode of action of sulfonamides. It likewise has no bearing on the present invention.

Columns 13 and 14 contain a discussion of the use, in the screening method of Watson, et al., of a genetically altered strain of bacteria into which a lacZ reporter gene has been inserted. The present invention does not use bacteria that are genetically altered to express a reporter gene or anything else for that matter. Thus, columns 13 and 14 also have no bearing on the current invention.

Column 24, line 54, through column 26 relate to various studies that can be carried out with compounds after they have shown some activity in the Watson, et al, screen, i.e., the determination of their MICs and cytotoxicity. There also is a gratuitous paragraph laying claim to any compound that shows activity in the screen. The present invention is the diametric opposite of Watson, et al.; it relates to the use of known clinical antibiotics with known MICs and known cytotoxicity; the quotes from Watson, et al. simply do not apply.

The examples in column 29 – column 31, line 42 relate entirely to methods of testing compounds of unknown biological activity to determine if they in fact have any antimicrobial activity using E. coli cells genetically altered to express a LacZ reporter gene. As noted above, the present invention does not use genetically altered cells and is not concerned with testing compounds of totally unknown biological activity to see if they in fact have any.

The examiner is requested to withdraw the rejection.

35 USC § 103(a) rejection of claims 6 and 9- 15

The examiner has rejected claims 6 and 9 – 15 under § 103(a) as being unpatentable over Watson, et al., above, either alone or in view of Chen, et al., WO 99/18232. The examiner is of the opinion that "The reference teaches in column 29 various bacteria that includes species within the scope of the claimed bacterial cells of claim 3, a synthetase, see column 20 line 24 within the scope of claims 4, antibiotic tetracycline, see column 2, line 32 within the scope of claim 5; the use of ampicillin as an antibiotic, see column 23, line 4 and Watson, et al., teaches the use of visual means as well as conventional light meters to observe the color changes which renders claims 13 and 14 prima facie obvious to one of ordinary skill in the art." The examiner then

goes on to opine that "The reference to Watson, et al. does not teach the biological samples which would have been prima facie obvious to one of ordinary skilled (sic) in the art to employ in view of the teachings of Chen, et al., to employ as the test samples feces or tissues, see page 13 in particular. In addition Chen employs various fluorogenic as well as chromogenic substrates, which can be detected by various means, see pages 11 and 12. Chen also discloses essentially the same methods for determining the susceptibility of microorganisms to antibiotics." Applicant traverses.

Applicant's response

None of the Watson, et al., statements cited by the examiner is pertinent to the present invention. Column 29 is merely a shopping list of "infectious agents" that Watson, et al, claim will be susceptible to compounds revealed to have antimicrobial activity using their test. This bears no relationship to the present invention, which deals with the susceptibility of specific isolated, although not necessarily identified, microbial species to known, clinically approved drugs.

The reference to a "synthase" in column 20 line 24 is simply an identification of a component of an assay strain of E. coli being used in the screening of compounds. It likewise would have no meaning in relation to the present invention to one skilled in the art.

Tetracycline is indeed identified as an antibiotic, but only in relation to Watson et al.'s exposition of a means for overcoming resistance to it using another compound that attacks the resistance mechanism. This again has nothing to do with the present invention which does not address how to overcome resistance but, rather, merely how to identify it in an extremely rapid, clinically useful manner.

The color changes described in Watson, et al., are related to a reporter gene genetically added to E. coli bacteria; such procedure has no nexus to the present invention which is concerned with histochemical reagents that react with normal products of an enzymatic reaction in a biochemical pathway.

In short, Watson, et al., has no bearing on the present invention which does not disclose or claim a method for screening compounds of unknown biological activity to see if they have antimicrobial activity. The compounds used in the present invention are known clinical antibiotic agents. The purpose of the test of the present invention is

to determine whether a particular organism – the identity of which need not be known – which has infected a patient is or is not susceptible to a particular antibiotic. The purpose of the test is to permit very rapid identification of an antibiotic that is effective against a particular invading organism and thus avoid the need to use broad spectrum antibiotics as an interim measure to control an infection while an appropriate specific antibiotic is found using current lengthy (24 hours or more) test procedures. Avoidance of broad spectrum antibiotics is beneficial in that their use is thought to contribute to the disconcerting increase in resistant species. Watson, et al., do the opposite, i.e., they use a known bacteria, E. coli, genetically altered to express a reporter gene, to test compounds of unknown biological activity to determine if they are antimicrobials at all.

As for Chen, et al., they merely disclose an alternative means of testing antibiotic susceptibility that still employs the current lengthy incubation procedure that uses the growth of a target species of bacteria as the measure thereof. Like Watson (and other versions of the current practice) Chen requires 24 hours incubation, which, as explained by applicant in the specification, is too long to wait to attack an invading pathogen, where time is of the essence. Applicant's test can be performed in a little over an hour and on as few as a single bacterium (although such would not normally be the case since isolation of the organism from a patient would generally provide a fairly substantial number of bacteria) whose growth and proliferation characteristics are irrelevant to the outcome. If the selected biochemical pathway is inhibited, no staining will be observed and the antibiotic can be administered by the clinician with confidence of its efficacy.

CONCLUSION

Based on the amendments attached hereto and above remarks, applicants believe that the application is in condition for allowance and respectfully requests that it be passed to issue.

Applicant requests a three month extension . The Commissioner is authorized to charge the amount due to Bingham McCutchen Deposit Account No. 50-2518, billing reference no. 2024748-2247487238.

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Date: December 2, 2003

Respectfully submitted,

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